EUROPEAN PATENT APPLICATION

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(54) CYCLIC AMINE DERIVATIVES.

(57) Compounds represented by general formula (I),
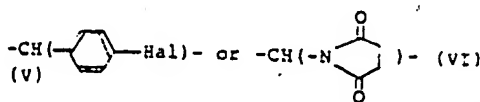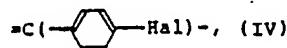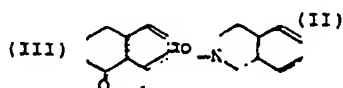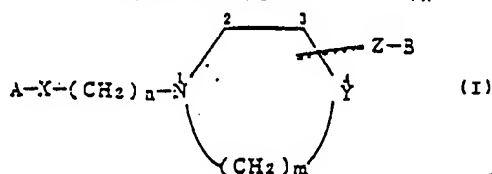
(wherein
A represents substituted or unsubstituted phenyl, pyridyl, thienyl, substituted or unsubstituted naphthyl, tetralyl, quin-

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olyl, benzofuranyl, quinazolyl, benzothienyl, a compound of formula (II) or (III); X represents $-CH_2-$, $-(C^1=O)-$, $-CH(OH)-$, $-CH(CH_3)-$ or $-CH(CH_2N(C_2H_5)_2)-$; n represents an integer of 0 to 4; m represents an integer of 1 to 3; Y represents a carbon or nitrogen atom; Z represents $-CH_2-$, $-C(=O)-$, $CH(OR^1)-$, (wherein R^1 represents H, lower alkyl, acyl, arylalkyl or heteroarylalkyl), $-CH(Hal)-$, $=CH-$, a compound of formula (IV), (V) or (VI); Hal represents a halogen atom; a symbol between Y and Z represents a single or double bond, and a group   Z   B is bound to the ring at the 3- or 4-position of the above structural formula; B represents a phenyl or naphthyl group optionally substituted by one or two of the same or different substituents selected from among halogen, lower alkyl, and lower alkoxy) and salts. They are effective for retrieval, therapy and prophylaxis of mental troubles accompanying brain blood vessel troubles.

SPECIFICATION

CYCLIC AMINE DERIVATIVES

Field of Industrial Utilization:

5   The present invention relates to cyclic amine
derivatives having excellent medicinal activities.

Prior Art:

Various medicines for cerebral vascular dis-
orders have been proposed. For example, cerebral

10   vasodilator drugs and cerebral metabolism activators
have been used. However, no drug which is drastically
effective has been proposed as yet. At present,
there is no drug effective particularly for cerebral
vascular dementia and intellectual function dis-

15   orders among the symptoms due to cerebral vascular
disorders.

Object of the Invention:
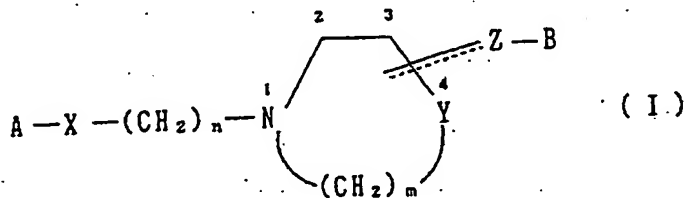
After intensive investigations made for the pur-
pose of finding a new compound effective for the

20   treatment of various symptoms due to cerebral vas-
cular disorders, particularly mental symptoms, over
a long time under the above-mentioned circumstances,
the inventors have found quite effective compounds.
The present invention has been completed on the basis

25   of this finding.

Therefore, an object of the present invention is to provide cyclic amine derivatives and pharmacologically acceptable salts thereof which are effective for the treatment of cerebral vascular

5 disorders such as cerebral stroke, apoplexy, infarction and arteriosclerosis and mental symptoms due to multiple infarct dementia. Another object of the invention is to provide a process for producing said compounds or pharmacologically acceptable salts

10 thereof. Still another object of the invention is to provide medicines containing said compound or pharmacologically acceptable salt thereof as the active ingredient.

Construction and Effect of the Invention:

15 The intended compounds of the present invention are cyclic amine derivatives of the general formula (I) or pharmacologically acceptable salts thereof:

20
$$A - X - (CH_2)_n - N \underset{(CH_2)_m}{\overset{2 \quad 3}{\diagup}} \overset{Z - B}{\underset{4}{\diagdown}} Y \qquad (I)$$

wherein A represents a substituted or unsubstituted phenyl, pyridyl or thienyl group, sub-

25 stituted or unsubstituted naphthyl, tetralyl,

quinolyl, benzofuranyl, quinazolyl or

benzothienyl group or a group of the formula:

    or   ,

X represents a group of the formula:

$$-CH_2-, \quad -\overset{\overset{\textstyle O}{\|}}{C}-, \quad -\overset{\overset{\textstyle OH}{|}}{C}H-, \quad -\overset{\overset{\textstyle CH_3}{|}}{C}H- \quad \text{or} \quad \overset{\textstyle CH_2}{\underset{\textstyle -CH-}{}}N\overset{\textstyle C_2H_5}{\underset{\textstyle C_2H_5}{}} ,$$
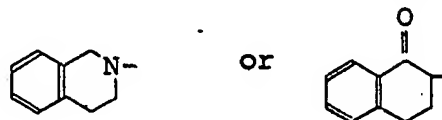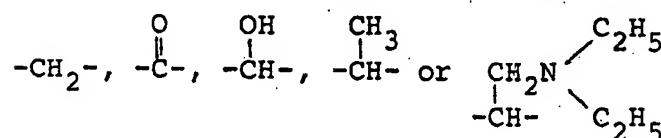
$\underline{n}$ represents an integer of 0 to 4,
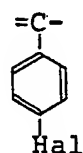
$\underline{m}$ represents an integer of 1 to 3,
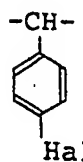
Y represents a carbon or nitrogen atom,

Z represents a group of the formula: $-CH_2-$,

$-\overset{\overset{\textstyle O}{\|}}{C}-, \quad -\overset{\overset{\textstyle OR^1}{|}}{C}H-$ in which R^1 is a hydrogen atom or a

lower alkyl, acyl, arylalkyl or heteroarylalkyl

group, $-\overset{\overset{\textstyle Hal}{|}}{C}H-$ in which Hal is a halogen atom,

$=CH-$, in which Hal is a halogen atom,

 in which Hal is a halogen atom or

 ,

the symbol "_____" between Y and Z represents

a single or double bond,

the group of the formula: "_____ Z-B" is

bonded with the ring in the above formula at

the 3- or 4-position, and
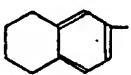
B represents a phenyl or naphthyl group which

may be substituted with one or two substituents

which may be the same or different and which

are selected from the group consisting of

halogens, lower alkyl groups and lower alkoxy

groups.

The lower alkyl groups in the above-mentioned

definitions of R^1 and B include, for example,

straight-chain or branched alkyl groups having 1 to

6 carbon atoms such as methyl, ethyl, n-propyl,

n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-

butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl

groups. Among them, methyl and ethyl groups are the

most preferred.

The lower alkoxy groups in the above-mentioned

definition of B are those derived from the above-

mentioned lower alkyl groups. Preferred examples of

them include methoxy, ethoxy, propoxy, isopropoxy,

butoxy and isobutoxy groups.

The substituents of the "substituted or

unsubstituted phenyl group" and "substituted or
unsubstituted naphthyl group" in the definition of
A include, for example, the above-defined lower
alkyl and alkoxy groups, hydroxyl group, halogen
atoms such as fluorine, bromine, iodine and chlo-
rine, phenyl group and heterocyclic groups having
nitrogen atom(s) as the hetero atom such as imida-
zolyl, pyridyl and pyrazolyl groups. Said compounds
may have one to three of these substituents. When
the compound have two or more of these substituents,
they may be the same or different.

The phenyl group may have a methylenedioxy or
ethylenedioxy group bonded with two different carbon
atoms constituting the phenyl ring in addition to
the above-mentioned substituents. Further, the sub-
stituted phenyl group include also a group of the

formula:

The acyl groups in the definition of R^1 include
organic acid residues such as saturated aliphatic,
unsaturated aliphatic, carbocyclic and heterocyclic
carboxylic acid residues. Examples of them include
lower alkanoyl groups such as formyl, acetyl, pro-
pionyl, butyryl, isobutyryl, valeryl, isovaleryl and
pivaloyl groups, aroyl groups such as benzoyl, toluoyl

and naphthoyl groups and heteroaroyl groups such as furoyl, nicotinoyl and isonicotinoyl groups.

The arylalkyl groups in the definition of R^1 include, for example, those derived from substituted or unsubstituted phenyl and naphthyl groups. Typical examples of them include benzyl and phenethyl groups. The substituents in the above definition include, for example, the above-defined lower alkyl and lower alkoxy groups, hydroxyl group and halogen atoms such as fluorine, bromine, iodine and chlorine atoms.

Typical examples of the heteroarylalkyl groups include pyridylalkyl groups such as picolyl group.

The halogen atoms include fluorine, chlorine, bromine and iodine atoms.

The phamacologically acceptable salts are ordinary non-toxic salts, for example, inorganic acid salts such as hydrochlorides, hydrobromides, sulfates and phosphates; organic acid salts such as acetates, maleates, tartrates, methanesulfonates, benzenesulfonates and toluenesulfonates; and amino acid salts such as arginine salts, aspartates and glutamates.

Production processes

The compounds of the present invention can be

produced by various processes. A typical example

of these processes comprises:

$$A - X - (CH_2)_{\overline{n-1}} - CH_2 - Hal \qquad (II)$$

5

$$+$$

$$
\begin{array}{c}
\text{(structure with positions 2, 3 labeled, } Z-B, \\
\text{HN at position 1, Y at position 4, } (CH_2)_m)
\end{array}
\qquad (III)
$$

10

$$\downarrow$$

15

$$A - X - (CH_2)_n - N \quad \text{(ring with positions 2, 3, } Z-B, \text{ Y at position 4, } (CH_2)_m) \qquad (I)$$
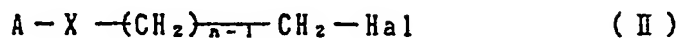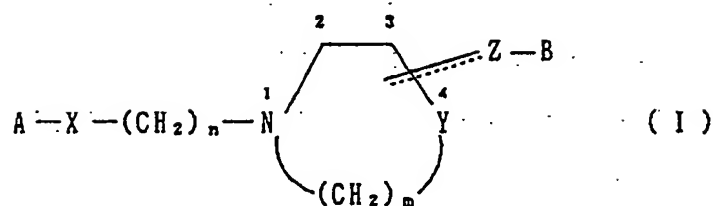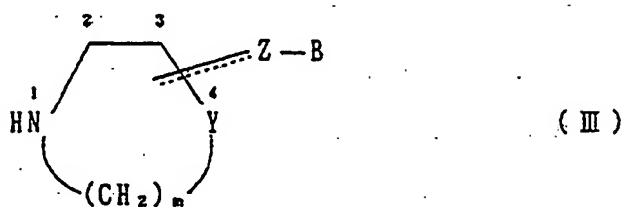
wherein Hal represents a halogen atom and A, X,

20   Y, Z, B, $\underline{n}$, $\underline{m}$ and ------ Z-B are as defined

above.

Namely, a halide of the general formula (II) is

reacted with a compound of the general formula (III)

to obtain an intended compound of the general formula

25   (I).

The dehydrohalogenation reaction is carried out
by heating in an ordinary manner without using any
solvent or in an organic solvent inert to the reac-
tion which is selected from the group consisting of
alcoholic solvents such as methanol, ethanol and
butanol, benzene, toluene, xylene, tetrahydrofuran,
chloroform, carbon tetrachloride and dimethylform-
amide. Preferred results are obtained when the
reaction is carried out in the presence of an in-
organic salt such as sodium hydrogencarbonate,
potassium carbonate, sodium carbonate or sodium
hydroxide or an organic base such as triethylamine,
pyridine, pyrimidine or diethylaniline.

It is apparent from the pharmacological experi-
ments described below that the compounds of the pre-
sent invention have excellent pharmacological effects
on the central nervous system, particularly a remark-
able reparative effect on ischemic cerebral vascular
disorders. Therefore, these compounds are useful
for relieving, remedying or preventing mental dis-
orders due to the cerebral vascular disorders such
as cerebral stroke, apoplexy, infarction, arterio-
sclerosis and dementias, e.g. multiple infarct
dementia.

It has been found in toxicity tests effected

by using rats that the compounds of the present

invention have a high safety and, therefore, the

invention is highly valuable also in this regard.

According to the toxicity tests of typical

5   compounds of the present invention (see Examples 1

to 12 given below), LD_{50} of them was 2,000 to 4,000

mg/kg (oral administration to rats).

The compounds of the present invention used as

the medicine are given either orally or parenterally.

10   The dose of said compounds is not particularly

limited, since it varies depending on the symptoms;

age, sex, body weight and sensitivity of the patient;

period and intervals of the administration; pro-

perties, composition and kind of the medicinal pre-

15   paration; and varieties of active ingredients.

Usually, about 0.1 to 300 mg/day, preferably about

1 to 100 mg/day of the compound is administered 1 to

4 times a day.

The compounds of the present invention are used

20   in the form of a medicinal preparation such as an

injection, suppository, sublingual tablet, tablet or

capsule.

In the preparation of the injection, a pH

adjustor, buffer, suspending agent, solubilizer,

25   stabilizer, isotonizer, preservative, etc. are added

to the active ingredient to form an intravenous, subcutaneous or intramuscular injection by an ordinary method. If necessary, the injection can be freeze-dried by an ordinary method.

5 Examples of the suspending agents include methylcellulose, Polysorvate 80, hydroxyethylcellulose, acacia, tragacanth gum powder, sodium carboxymethylcellulose and polyoxyethylenesorbitan monolaurate.

10 Examples of the solubilizers include polyoxyethylene hardened castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, macrogol and ethyl esters of castor oil fatty acids.

Examples of the stabilizers include sodium

15 sulfite, sodium metasulfite and ether. Examples of the preservatives include methyl hydroxybenzoate, ethyl hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

[Examples]

20 Typical examples of the compounds of the present invention will be shown below for facilitating the understanding of the present invention, which by no means limit the scope of the invention.

Example 1

25 2-{2-[4-(p-Fluorobenzyl)piperidinyl]ethyl}naphthalene

hydrochloride:
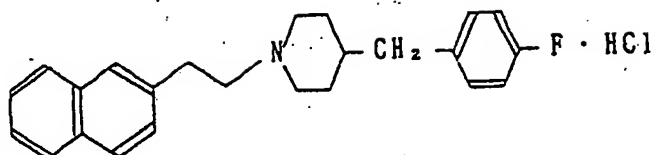
1.05 g of 1-chloro-2-(2-naphthyl)ethane, 1.09
g of 4-(p-fluorobenzyl)piperidine, 0.2 g of potassium
iodide and 1.4 g of sodium hydrogencarbonate were
refluxed in n-butanol solvent for 5 h. Then, the
solvent was filtered out and 100 mℓ of chloroform
was added to the residue. The mixture was washed
with water and dried over magnesium sulfate. The
oily product thus obtained was purified according to
silica gel column chromatography and converted into
its hydrochloride by an ordinary method.

Yield: 0.45 g

Melting point: 244°C

Elementary analysis for $C_{24}H_{26}NF \cdot HCl$:

	C	H	N
calculated (%):	75.08	7.09	3.65
found (%):	75.30	7.32	7.34

Example 2

2-(4-Benzylpiperidinyl)-2'-acetonaphthone hydro-
chloride:

$$\text{(structure: 2-naphthyl—C(=O)—CH}_2\text{—N-piperidine—4-CH}_2\text{—phenyl)} \cdot \text{HCl}$$
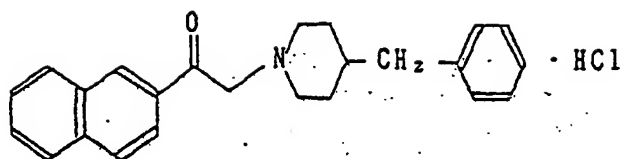
5 5 g of 2-bromo-2'-acetonaphthone, 3.5 g of 4-benzylpiperidine, 0.2 g of potassium iodine and 5 g of sodium hydrogencarbonate were refluxed in butanol solvent for 4 h. After completion of the reaction, the product was treated by an ordinary

10 process. The oily product thus obtained was purified according to silica gel column chromatography and converted into its hydrochloride, which was then recrystallized from chloroform and ethanol.

Yield: 2.1 g

15 Melting point: 233 to 235°C

Elementary analysis for $C_{24}H_{25}NO \cdot HCl$:

	C	H	N
calculated (%)	75.87	6.90	3.69
found (%)	75.67	6.71	3.49

20 Example 3

2-[4-Bis(4-fluorophenyl)methylene-1-piperidinyl]-
2'-acetonaphthone hydrochloride:
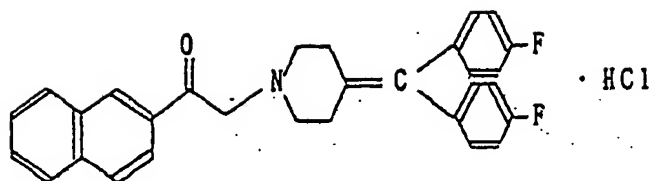
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850 mg of 4-bis(4-fluorophenyl)methylene-
piperidine, 700 mg of 2-bromo-2'-acetonaphthone,
20 mg of potassium iodide and 760 mg of sodium
hydrogencarbonate were refluxed in n-butanol solvent
for 3.5 h. After completion of the reaction, the
product was treated by an ordinary process. The
obtained oily product was purified according to
silica gel column chromatography and converted into
its hydrochloride to obtain 510 mg of the intended
product.

Melting point: 214 to 217°C

Elementary analysis for $C_{30}H_{25}NOF_2 \cdot HCl$

	C	H	N
calculated (%):	73.54	5.35	2.86
found (%):	73.54	5.46	3.03

Example 4

4-(1-Naphthonyl)piperidinyl-3',4'-dimethylaceto-
phenone hydrochloride:
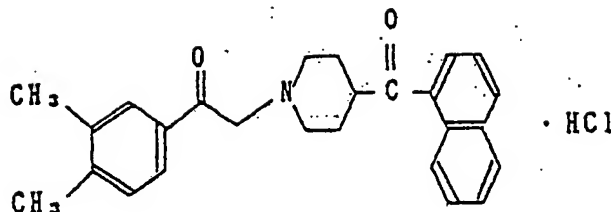
1.9 g of 2-bromo-3',4'-dimethylacetophenone,

2.0 g of 4-(1-naphthonyl)piperidine, 0.1 g of potas-

sium iodide and 2.1 g of sodium hydrogencarbonate

were refluxed in n-butanol solvent for 3 h. After

completion of the reaction, the product was treated

by an ordinary process. The obtained oily product

was purified according to silica gel column chro-

matography and converted into its hydrochloride to

obtain 1.0 g of the intended product.

Melting point: 92 to 96°C (dec.)

Elementary analysis for $C_{26}H_{27}NO_2 \cdot HCl$:

	C	H	N
calculated (%)	74.01	6.68	3.32
found (%)	73.79	6.69	3.01

Example 5

1-[3-(p-Fluorobenzoyl)piperidinyl]-2'-acetonaphthone
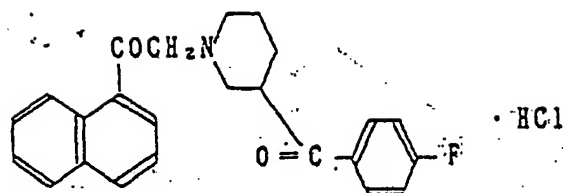
hydrochloride:

0.7 g of 1-bromo-2'-acetonaphthone, 0.7 g of

3-(p-fluorobenzoyl)piperidine hydrochloride, 0.05 g

of potassium iodide and 0.7 g of sodium hydrogen-

carbonate were refluxed in n-butanol solvent for 2 h.

After completion of the reaction, the product was

treated by an ordinary process. The obtained oily

product was purified according to silica gel column

chromatography and converted into its hydrochloride.

Yield: 0.4 g

Melting point: 123 to 127°C (dec.)

Elementary analysis for $C_{24}H_{22}NO_2F \cdot HCl$:

	C	H	N
calculated (%)	69.98	5.63	3.40
found (%)	69.76	5.51	3.18

Example 6

2-[4-(α-Benzyloxy-p-fluorobenzyl)piperidinyl]-2'-

acetonaphthone hydrochloride:

1.1 g of 2-bromo-2'-acetonaphthone, 1.2 g of

4-(α-benzyloxy-p-fluorobenzyl)piperidine and 4.5 g

of sodium hydrogencarbonate were refluxed in ethanol

solvent for 3.5 h. After completion of the reaction,

the product was treated by an ordinary process.

The oily product thus obtained was purified according

to silica gel column chromatography and converted

into its hydrochloride, which was recrystallized

from ethyl acetate/methanol.

Yield: 0.6 g

Melting point: 115 to 120°C

Elementary analysis for $C_{31}H_{30}NO_2F \cdot HCl$:

	C	H	N
calculated (%)	76.76	6.44	2.89
found (%)	76.59	6.21	2.68

Example 7

2-[4-(α-Acetoxy-p-fluorobenzyl)piperidinyl]-2'-

acetonaphthone hydrochloride
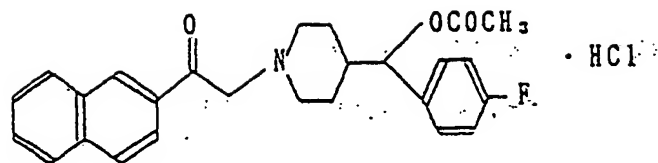
5.4 g of 2-bromo-2'-acetonaphthone, 4.6 g of
4-(α-hydroxy-p-fluorobenzyl)piperidine and 10 g of
sodium hydrogencarbonate were refluxed in ethanol
solvent for 2.5 h. After completion of the reaction,
the product was treated by an ordinary process.
The obtained oily product was purified according to
silica gel column chromatography to obtain 5 g of
2-[4-(α-hydroxy-p-fluorobenzyl)piperidinyl]-2'-
acetonaphthone. 1 g of this product was stirred
together with 1.0 g of acetic anhydride and 0.1 g of
dimethylaminopyridine in pyridine solvent at room
temperature for 5 h. After completion of the reac-
tion, the oily product was purified according to
silica gel column chromatography and converted into
its hydrochloride, which was recrystallized from
ethyl acetate and methanol.

Yield: 1.0 g

Melting point: 148 to 152°C

Elementary analysis for $C_{26}H_{26}NO_3F \cdot HCl$:

	C	H	N
calculated (%)	68.49	5.97	3.07
found (%)	68.24	5.88	3.12

Example 8

4-(4-p-Fluorobenzoyl)piperidinyl-6,7-dimethoxyiso-
quinoline hydrochloride
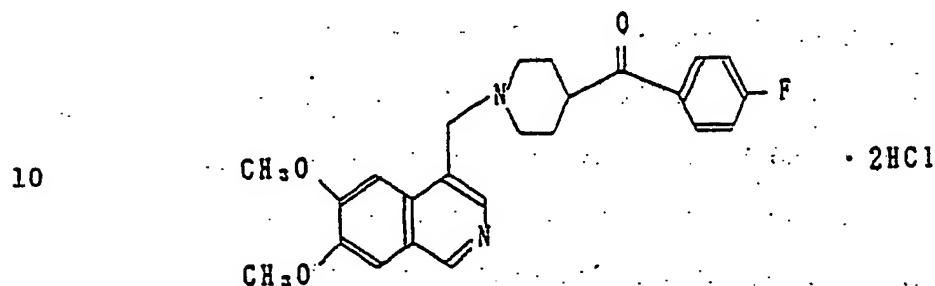
70 mg of 4-chloromethyl-6,7-dimethoxyisoquino-
line was dissolved in 10 mℓ of dimethyl sulfoxide.
1 mℓ of triethylamine and 140 mg of 4-(p-fluoroben-
zoyl)piperidine were added to the solution and the
mixture was heated to 80°C for 1 h. The reaction
mixture was dissolved in ethyl acetate, washed with
water and dried over magnesium sulfate. The product
was purified according to silica gel column chro-
matography and converted into its hydrochloride.
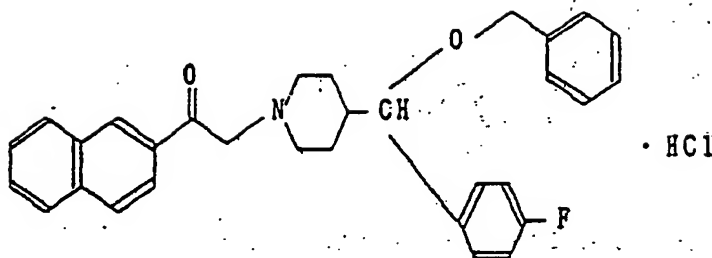
Yield: 80 mg

Melting point: 185 to 190°C

Elementary analysis for $C_{24}H_{25}N_2O_3F \cdot 2HCl$:

	C	H	N
calculated (%)	59.88	5.65	5.82
found (%)	59.78	5.61	5.80

Example 9

4-{2-[4-(p-Fluorobenzoyl)piperidinyl]ethyl}quinazoline

hydrochloride
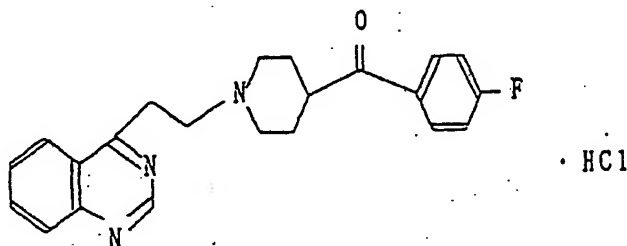
2 g of 4-methylquinazoline was dissolved in 20 mℓ of ethanol. 3.4 g of 4-(p-fluorobenzoyl)-piperidine hydrochloride and 1.9 mℓ of 37% formalin were added to the solution and the mixture was stirred at room temperature for three days. A white precipitate was recovered by filtration and washed with ethanol to obtain the intended product.

Yield: 4.4 g

Melting point: 135 to 140°C

Elementary analysis for $C_{22}H_{22}N_3OF \cdot HCl$:

	C	H	N
calculated (%)	66.08	5.79	10.51
found (%)	66.02	5.65	10.44

Example 10

1-(2-Naphthyl)-1-[4-(p-fluorobenzoyl)piperidinyl]-
2-diethylaminoethane hydrochloride:

5

· 2HCl
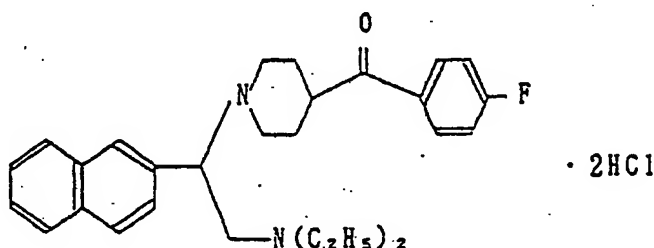
10   1.4 g of 1-(2-naphthyl)-2-diethylaminoethanol

was dissolved in 20 mℓ of dichloromethane. 2.4 mℓ

of triethylamine and 0.9 mℓ of methanesulfonyl

chloride were added to the solution under cooling

with ice and the mixture was stirred at room temper-

15   ature for 4.5 h. A solution of 1.2 g of 4-(p-fluoro-

benzoyl)piperidine in 25 mℓ of dioxane was added to

the reaction mixture and the obtained mixture was

refluxed for 2 h. After completion of the reaction,

the product was purified according to silica gel

20   column chromatography and then converted into its

hydrochloride.

Yield: 1.9 g

Melting point: 140 to 145°C

Elementary analysis for $C_{28}H_{33}N_2OF \cdot 2HCl$:

25

	C	H	N
calculated (%)	66.52	6.97	5.54
found (%)	66.57	6.81	5.38

Example 11

2-[4-(α-Succinimido-p-fluorobenzyl)piperidinyl]-

2'-acetonephthone hydrochloride
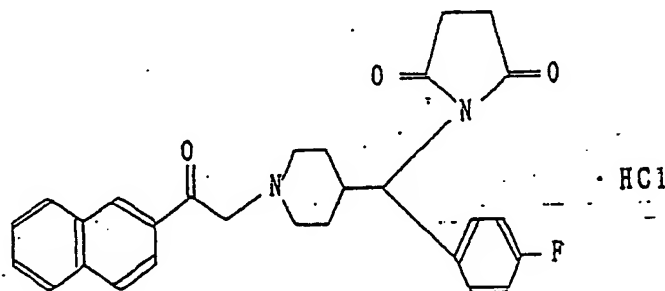
470 mg of 4-(α-succinimido-p-fluorobenzyl)-

piperidine was dissolved in 40 mℓ of ethanol. 410 mg

of 2-bromo-2'-acetonaphthone and 420 mg of sodium

hydrogencarbonate were added to the solution and the

mixture was refluxed for 30 min. After completion

of the reaction, the prodcut was treated by an

ordinary process. The obtained product was purified

according to silica gel column chromatography and

converted into its hydrochloride.

Yield: 400 mg

Melting point: 233 to 237°C

Elementary analysis for $C_{28}H_{27}N_2O_3F \cdot HCl$:

	C	H	N
calculated (%)	67.94	5.70	5.66
found (%)	68.13	5.56	5.47

Example 12

2-[4-p-Fluorobenzoyl)piperidinyl]-2'-acetonaphthone hydrochloride
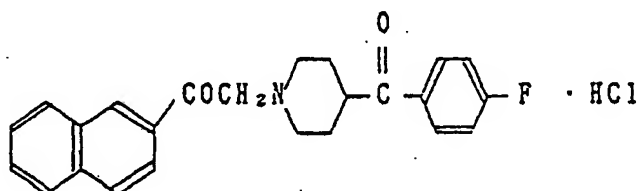
49.7 g of 2-bromo-2'-acetonaphthone, 49.9 g of 4-(p-fluorobenzoyl)piperidine hydrochloride, 0.5 g of potassium iodide and 50.4 g of sodium hydrogen-carbonate were added to 500 mℓ of ethanol and the mixture was refluxed for 2 h. The solvent was distilled off and chloroform was added to the residue. The mixture was washed with water and dried. Chloroform was distilled off and the residue was purified according to silica gel column chromatography to obtain 58.9 g of the crystalline intended product, which was converted into its hydrochloride and re-crystallized by an ordinary process to obtain the intended hydrochloride.

Melting point: 247 to 248°C (dec.)

Elementary analysis for $C_{24}H_{22}NO_2F \cdot HCl$:

	C	H	N
calculated (%)	69.98	5.63	3.40
found (%)	69.81	5.51	3.36

5 Examples 13 to 95

Compounds shown in Table 1 were prepared in the same manner as in Examples 1 to 12.

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Table 1

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
13	F—◯—CONH—◯—⟨N⟩—C(=O)—◯—F · HCl	234~235 (dec.)	$C_{20}H_{23}N_2O_2F_2 \cdot HCl$	61.68 61.49	5.92 5.85	6.85 6.77
14	◯—CH(OH)—CH₂—⟨N⟩—C(=O)—◯—F · HCl	216~218 (dec.)	$C_{20}H_{22}NO_2F \cdot HCl$	66.02 66.16	6.37 6.39	3.85 3.77
15	F—◯—C(=O)—⟨N⟩—C(=O)—◯—F · HCl	228~229 (dec.)	$C_{20}H_{19}NO_2F_2 \cdot HCl$	63.24 63.11	5.31 5.37	3.69 3.58
16	F—◯—C(=O)—⟨N⟩—◯—F · HCl	223~224 (dec.)	$C_{20}H_{21}NOF_2 \cdot HCl$	65.66 65.39	6.06 6.12	3.83 3.81
17	CH₃O—◯—⟨N⟩—C(=O)—◯—F · HCl	225~226 (dec.)	$C_{21}H_{24}NO_2 \cdot HCl$	70.28 69.97	7.02 7.13	3.90 3.88
18	CH₃O—◯—⟨N⟩—CH₂—◯ · HCl	201~202	$C_{21}H_{27}NO \cdot HCl$	72.92 72.76	8.16 8.23	4.05 4.11

Table 1 (cont'd)
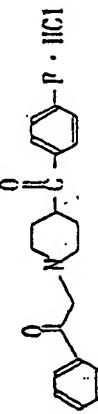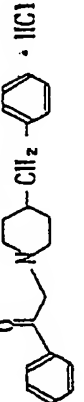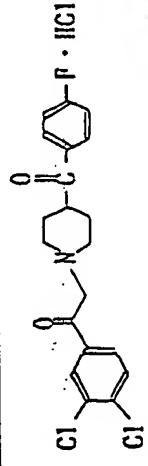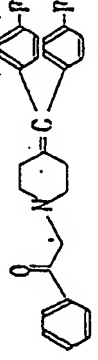
Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
1 9	[structural formula]	233~235 (dec.)	$C_{20}H_{20}NO_2P \cdot HCl$	66.38 66.27	5.85 5.82	3.87 3.85
2 0	[structural formula]	244~245	$C_{22}H_{24}NO_2P \cdot HCl$	67.77 67.80	6.46 6.47	3.59 3.57
2 1	[structural formula]	211~211.5	$C_{20}H_{23}NO \cdot HCl$	72.82 72.19	7.33 7.13	4.25 4.12
2 2	[structural formula]	222~223 (dec.)	$C_{20}H_{19}NO_2PCl_2 \cdot 2HCl$	55.75 55.71	4.44 4.50	3.25 3.26
2 3	[structural formula]	235~236	$C_{22}H_{24}NOP_2 \cdot HCl$	70.98 70.59	5.50 5.63	3.18 3.34

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
2 4		143~146	$C_{24}H_{25}NO_2 \cdot HCl$	70.66 / 70.43	5.93 / 5.91	3.17 / 3.24
2 5		65~69	$C_{22}H_{24}NO_4P \cdot HCl$	62.63 / 62.48	5.97 / 5.70	3.39 / 3.11
2 6		234~236 (dec.)	$C_{22}H_{24}NO_4P \cdot HCl$	62.63 / 62.57	5.97 / 5.96	3.32 / 3.15
2 7		223~226 (dec.)	$C_{19}H_{21}N_2OP \cdot 2HCl$	59.23 / 59.18	6.02 / 6.11	7.27 / 7.02
2 8		155~160 (dec.)	$C_{19}H_{21}N_2OP \cdot 2HCl$	57.91 / 57.80	6.21 / 6.12	7.50 / 7.20

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
2 9	CH2—N⬡—⬡—C(=O)—⬡—F · 2HCl	220~225 (dec.)	$C_{19}H_{19}N_2OF \cdot 2HCl$	58.23 58.25	5.70 5.71	7.55 7.43
3 0	CH2—N⬡—⬡—C(=O)—naphthyl · 2HCl	121~125 (dec.)	$C_{22}H_{22}N_2O \cdot 2HCl$	63.01 62.91	5.77 5.73	6.68 6.59
3 1	biphenyl—O—(CH2)—N⬡—C(=O)—⬡—F · HCl	238~240	$C_{27}H_{28}NO_2F \cdot HCl$	71.42 71.13	6.44 6.29	3.09 3.10
3 2	⬡—CH2—N⬡—CH2—⬡ · HCl	173~174	$C_{19}H_{22}N_2O \cdot HCl$	68.98 68.75	7.01 6.89	8.47 8.26
3 3	thienyl—C(=O)—⬡—N⬡—C(=O)—⬡—F · HCl	243~244	$C_{19}H_{19}NO_2F \cdot HCl$	58.77 58.61	5.21 5.51	3.91 3.91

Table 1 (cont'd)

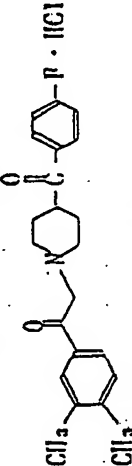| Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
3 4	(structural formula, terminating F · HCl)	253~254 (dec.)	$C_{24}H_{24}NO_2F \cdot HCl$	71.31 71.51	5.75 6.03	3.20 3.25
3 5	(structural formula, terminating F · 2HCl)	269~270 (dec.)	$C_{23}H_{23}N_3O_2F \cdot 2HCl$	59.36 59.23	5.41 5.40	9.03 9.11
3 6	(structural formula, terminating F · HCl)	182~184 (dec.)	$C_{25}H_{25}N_2O_2F \cdot HCl$	68.10 68.31	5.94 5.96	6.35 6.22
3 7	(structural formula, terminating OCH₃ · HCl)	232~234 (dec.)	$C_{25}H_{25}NO_3 \cdot HCl$	70.83 70.76	6.18 6.09	3.30 3.21
3 8	(structural formula, terminating Cl · HCl)	242~244 (dec.)	$C_{24}H_{22}NO_2Cl \cdot HCl$	67.30 67.22	5.41 5.35	3.27 3.31

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
3 9	(naphthyl–CH₂CH₂–N piperidine–CO–〈 〉–P · HCl)	253~255 (dec.)	C₂₄H₂₄NO₂P · HCl	72.44 / 72.40	6.33 / 6.38	3.52 / 3.49
4 0	(naphthyl–N piperidine–CO–〈 〉–P · 2HCl)	199~200 (dec.)	C₂₄H₂₉N₂O₂P · 2HCl	63.57 / 63.47	6.89 / 6.78	6.18 / 6.26
4 1	(CH₃O, CH₃O substituted–N piperidine–CH(OH)–〈 〉–P · 2HCl)	198~200 (dec.)	C₂₄H₃₅N₂O₄P · 2HCl	60.58 / 60.43	7.24 / 7.12	5.44 / 5.63
4 2	(naphthyl–CO–O–CH₂ –N piperidine–CO–〈 〉–P · HCl)	209~210 (dec.)	C₂₅H₂₄NO₃P · HCl	67.94 / 68.01	5.70 / 5.81	3.17 / 3.01
4 3	(naphthyl–S–CH₂CH₂CH₂–N piperidine–CO–〈 〉–P · HCl)	195~196 (dec.)	C₂₅H₂₄NOSP · HCl	67.62 / 67.82	6.13 / 6.17	3.15 / 2.89

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
44	(structural formula)	253~254 (dec.)	$C_{22}H_{21}NO_4P \cdot HCl$	63.08 63.16	5.29 5.36	3.34 3.32
45	(structural formula)	180~181	$C_{23}H_{24}NO_2P \cdot HCl$	68.73 68.88	6.27 6.32	3.49 3.39
46	(structural formula)	209~210 (dec.)	$C_{25}H_{24}NO_2P \cdot HCl$	70.49 70.40	5.92 5.85	3.29 3.35
47	(structural formula)	266~267 (dec.)	$C_{25}H_{34}N_2O_2 \cdot 2HCl$	64.23 64.36	7.76 7.72	5.99 6.11
48	(structural formula)	214~217 (dec.)	$C_{22}H_{21}N_2OP \cdot 2HCl$	62.71 62.77	5.50 5.43	6.65 6.72

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
4 9	(structure · 2HCl)	260~263 (dec.)	$C_{23}H_{23}N_2OP \cdot 2HCl$	63.45 63.16	5.79 5.81	6.43 6.36
5 0	(structure · HCl)	236~237 (dec.)	$C_{25}H_{24}NO_2P \cdot HCl$	70.50 70.31	5.92 5.86	3.29 3.31
5 1	(structure · HCl)	242 (dec.)	$C_{25}H_{24}NO_2P \cdot HCl$	70.50 70.37	5.92 5.96	3.29 3.31
5 2	(structure · HCl)	237~238 (dec.)	$C_{24}H_{22}NOP \cdot HCl$	71.96 71.88	6.04 6.12	3.65 3.57
5 3	(structure · HCl)	231~232 (dec.)	$C_{24}H_{24}NO_2Cl \cdot HCl$	69.57 69.48	6.08 6.16	3.38 3.42

Table 1 (cont'd)
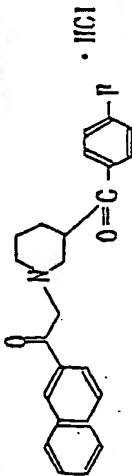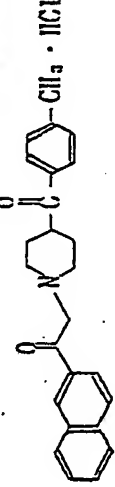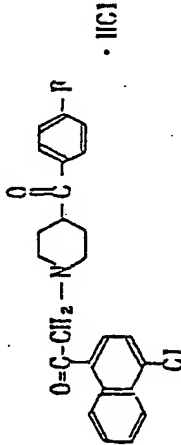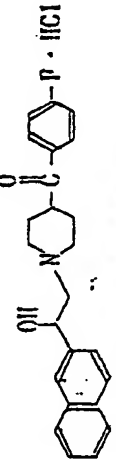
Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
5 4		153~156	$C_{24}H_{22}NO_2F \cdot HCl$	69.98 / 70.12	5.63 / 5.58	3.40 / 3.26
5 5		222~225 (dec.)	$C_{25}H_{27}NO \cdot HCl$	76.22 / 75.93	7.16 / 7.33	3.56 / 3.47
5 6		250~253 (dec.)	$C_{25}H_{25}NO_2 \cdot HCl$	73.61 / 73.48	6.42 / 6.33	3.43 / 3.19
5 7		256~260 (dec.)	$C_{24}H_{21}NO_2ClF \cdot HCl$	67.45 / 67.18	5.19 / 5.06	3.28 / 3.14
5 8		246~248 (dec.)	$C_{24}H_{24}NO_2F \cdot HCl$	69.64 / 69.61	6.08 / 6.02	3.38 / 3.14

Table 1 (cont'd)

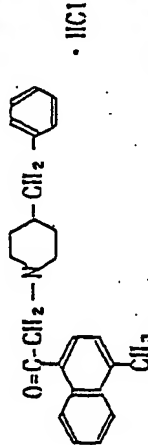| Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
5 9	(structure)	250~254 (dec.)	$C_{24}H_{26}NO_2P \cdot HCl$	70.98 70.96	6.19 6.14	3.18 3.20
6 0	(structure)	223~226 (dec.)	$C_{24}H_{22}NO_2P \cdot HCl$	69.98 69.86	5.63 5.58	3.40 3.22
6 1	(structure)	272~274 (dec.)	$C_{22}H_{27}NOP \cdot HCl$	62.87 62.69	6.65 6.54	6.38 6.28
6 2	(structure)	214~217 (dec.)	$C_{23}H_{25}N_2O_2P \cdot HCl$	66.26 66.13	6.29 6.25	6.72 6.47
6 3	(structure)	263~266 (dec.)	$C_{23}H_{26}NO_2P \cdot HCl$	68.39 68.18	6.74 6.55	3.47 3.41
6 4	(structure)	234~238 (dec.)	$C_{21}H_{22}N_3P \cdot 3HCl$	56.71 56.45	5.66 5.58	9.45 9.17

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
6 5	(structure with quinoline, piperazine, C=O, C₆H₄F · 2HCl)	230~233 (dec.)	$C_{21}H_{20}N_3OF \cdot 2HCl$	59.73 / 59.54	5.25 / 5.13	9.94 / 9.78
6 6	(structure with naphthalene, piperidine, OC₂H₅, C₆H₄F · HCl)	142~147	$C_{24}H_{28}NO_2F \cdot HCl$	70.66 / 70.53	6.61 / 6.50	3.17 / 3.06
6 7	(structure with naphthalene, piperidine, CH–O–CH₂–phenyl, C₆H₄F · 2HCl)	98~104	$C_{30}H_{29}N_2O_2F \cdot 2HCl$	66.54 / 66.42	5.77 / 5.68	5.17 / 5.07
6 8	(structure with benzodioxane, piperidine, O=C, C₆H₄F · HCl)	135~140	$C_{22}H_{22}NO_4F \cdot HCl$	62.93 / 62.69	5.52 / 5.41	3.34 / 3.17

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
69	(structural formula)	162~164	$C_{25}H_{24}NO_2F$	76.37 / 76.03	6.41 / 6.40	3.71 / 3.56
70	(structural formula)	236~237 (deg.)	$C_{31}H_{30}NO_2F \cdot HCl$	73.86 / 73.92	6.20 / 6.21	2.78 / 2.78
71	(structural formula)	242~245	$C_{24}H_{23}NO_2 \cdot HCl$	73.18 / 73.33	6.14 / 6.18	3.56 / 3.66
72	(structural formula)	182~183	$C_{25}H_{27}NO_2 \cdot HCl$	73.25 / 73.26	6.88 / 6.76	3.42 / 3.24

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
7 3	(structural formula) · HCl	222~223	$C_{24}H_{27}N \cdot HCl$	78.77 78.73	7.11 7.64	3.83 3.62
7 4	(structural formula) F · HCl	246~246.5	$C_{24}H_{22}NOF \cdot HCl$	72.81 72.66	5.81 5.70	3.54 3.45
7 5	(structural formula) F · HCl	243~244	$C_{24}H_{24}NOF \cdot HCl$	72.44 72.39	6.33 6.47	3.52 3.50
7 6	(structural formula) F · HCl	224~225	$C_{22}H_{20}NO_3F \cdot HCl$	65.75 65.79	5.27 5.26	3.49 3.36
7 7	(structural formula) F · HCl	206~207	$C_{23}H_{21}N_2O_2F \cdot HCl$	66.90 66.82	5.37 5.36	6.78 6.80

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
7 8	(naphthyl)CH(OH)—CH₂—N(piperidine)—CH—C₆H₄—P · HCl	173~174	$C_{24}H_{27}NO_2P \cdot HCl$	69.14 / 69.02	6.77 / 6.51	3.36 / 3.27
7 9	(naphthyl)CH(Cl)—CH₂—N(piperidine)—C(=O)—C₆H₄—P · HCl	187~188	$C_{24}H_{23}NOPCl \cdot HCl$	66.67 / 66.43	5.59 / 5.33	3.24 / 3.12
8 0	(naphthyl)CH₂—N(piperidine)—CH₂—C₆H₅ · HCl	172~173	$C_{23}H_{25}N \cdot HCl$	78.50 / 78.64	7.45 / 7.37	3.98 / 3.84
8 1	(naphthyl)CH₂CH₂—N(piperidine)—CH₂—C₆H₅ · HCl	226~227	$C_{24}H_{27}N \cdot HCl$	78.76 / 78.75	7.45 / 7.40	3.83 / 3.78
8 2	(naphthyl)CH₂CH₂—N(piperazine)—CH₂—C₆H₅ · 2HCl	274~275	$C_{23}H_{26}N_2 \cdot 2HCl$	68.48 / 68.52	7.00 / 7.02	6.94 / 6.87

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
8 3		249	$C_{24}H_{24}NF \cdot HCl$	75.48 75.44	6.60 6.45	3.67 3.82
8 4		203	$C_{24}H_{24}NOF \cdot HCl$	72.44 72.11	6.33 6.19	3.52 3.59
8 5		216~217	$C_{24}H_{27}NO \cdot HCl$	75.47 75.48	7.39 7.40	3.67 3.64
8 6		239~241	$C_{24}H_{23}NO \cdot HCl$	76.28 76.08	6.40 6.30	3.71 3.69
8 7		221~223	$C_{22}H_{23}NO_2 \cdot HCl$	71.44 71.16	6.54 6.58	3.79 4.03
8 8		227~229	$C_{20}H_{13}NO_2F \cdot HCl$	70.64 70.58	8.26 8.14	2.94 2.73

Table 1 (cont'd)

Example No.	Structural formula	Melting point (°C)	Chemical formula	Elementary analysis (%) calculated/found		
				C	H	N
8 9	CH₃ ... P · HCl	205~210 (dec.)	$C_{24}H_{24}NOP \cdot HCl$	72.44 / 72.41	6.33 / 6.19	3.52 / 3.41
9 0	CH₃ ... P · HCl	195~197 (dec.)	$C_{25}H_{25}NOP \cdot HCl$	72.89 / 72.83	6.60 / 6.54	3.40 / 3.37
9 1	... P · 2HCl	oily	$C_{19}H_{19}N_2O_2P \cdot 2HCl$	57.15 / 56.78	5.30 / 5.14	7.02 / 6.87
9 2	... · HCl · ¼H₂O	233.5~235	$C_{24}H_{25}NO \cdot HCl \cdot \tfrac{1}{4}H_2O$	74.98 / 74.90	6.95 / 6.92	3.64 / 3.69
9 3	Cl—CH ... P · HCl	oily	$C_{24}H_{23}NOPCl \cdot HCl$	66.67 / 66.39	5.59 / 5.62	3.24 / 3.24

The examples of pharmacological experiments of the compounds of the present invention will be given below:

Experimental Example 1

5   Effect of protecting ischemic brain

Carotid arteries of both sides of ICR mice (6 to 8 weeks old) were exposed under halothane anesthesia and ligated. The mice thus treated had stroke symptoms such as jumping, rolling and convul-
10   sion and almost all of them died within 24 h.

The compound of the present invention was administered orally to the mice one hour before the ligation and the survival time (maximum: 6 h) was examined as an index of the effect of protecting
15   eschemic brain. In this experiment, the compound was used in the form of a 5% suspension in acacia and a 5% acacia solution was given to the control group.

The results are shown in Table 2. It is apparent that the compounds of the present invention had a
20   life-prolonging effect, while the average survival time of the control group was 149.9 min.

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- 41 -

Table 2 Effect of protecting ischemic brain

Compound used	Dose (mg/kg, p.o.)	Number of cases	Average survival time (min) (average ± S.E.)	%
Control group	—	26	149.9 ± 25.8	100
Compound of Example 12	3	10	213.7 ± 52.3	143
	10	10	181.4 ± 43.6	121
	30	9	191.1 ± 54.3	128
Compound of Example 73	10	7	150.4 ± 57.6	100
	30	6	275.2 ± 58.2	184
Compound of Example 74	3	10	143.3 ± 39.6	96
	10	7	205.1 ± 43.6	137
	30	7	194.2 ± 49.7	130

Experimental Example 2

Effect of remedying learning disorder after ischemia

Common carotid arteries on both sides of
Mongolian gerbils (17 to 21 weeks old) were clipped

5 with Skoville clamps without anesthesia and the
clamps were removed after 5 min to realize a short
period of ischemia. Twenty-four hours after the
removal of the clamps, these animals were subjected
to learning and memory tests were conducted after

10 additional 24 h.

The learning and memory functions were examined
by the passive avoidance method with a modification
of a device reported by Jarvik & Kopp in "Psycholo-
gical Reports", 21, 221 to 224 (1967). The device

15 had two chambers, i.e. a well-lighted chamber A and
a dark chamber B. In the tests, the animals were
placed in the well-lighted chamber A and an electric
current (A.C., 1.6 mA) was applied to a grid on the
floor of the dark chamber B for 5 min when they

20 entered the chamber B.

On the next day, the animals subjected to the
learning were placed in the chamber A and the time
(latent time) which had elapsed before they entered
the chamber B was measured. The upper limit of the

25 latent time was set at 300 sec.

The compound was administered in the form of a
5% suspension in acacia orally one hour before caus-
ing the ischemia. A 5% acacia solution was admini-
stered to the control group.

5   The results are shown in Table 3. The average
latent time of the normal (pseudo-operation) group
was 246.5 sec and that of the control group was as
short as 71.5 sec. Namely, the learning and memory
functions of them were damaged by the 5-min ischemia.

10 When the compounds of the present invention were
administered to the control group, the latent time
was elongated again, namely the learning disorder
after the ischemia was remedied..

15

20

25

Table 3   Effects of remedying learning
disorder after ischemia

Compound used	Dose (mg/kg, p.o.)	Number of cases	Latent time (sec) (average ± S.E.)	Recovery ratio[*] (%)
Normal group	—	65	246.5 ± 10.9	100
Control group	—	62	71.5 ± 11.7	0
Compound of Example 12	3	22	168.8 ± 23.0	56
	10	24	196.8 ± 22.3	72
	30	11	196.3 ± 37.0	71
Compound of Example 73	10	8	193.1 ± 35.3	69
	30	7	80.1 ± 28.2	5
Compound of Example 74	3	13	110.2 ± 29.0	22
	10	24	123.2 ± 24.3	30
	30	21	129.2 ± 23.8	33

* The recovery ratio was calculated according to the

following formula for each latent time:

$$\frac{(\text{treated group}) - (\text{control group})}{(\text{normal group}) - (\text{control group})} \times 100$$

Experimental Example 3

Effect of protecting cells from disorder after

ischemia

Carotid arteries on both sides of Mongolian

5   gerbils were blocked to realize cerebral ischemia

for 5 min. As a result, the nerve cells in the CAI

region of the hippocampus disappeared extensively

[Karino, T.: Brain Res., 239, 57 to 69 (1982)].

The compound of the present invention was

10   administered orally to them, while a 5% acacia sus-

pension was administered to the control group. After

one hour, the ischemia was realized for 5 min. After

one week, the animal was perfused and fixed with 4%

neutral formalin transcardially. The treated sample

15   was embedded in paraffin and cut to obtain slices

having a thickness of 3 μm. The slices were dyed

with hematoxylin-eosin and the number of the nerve

cells in the CAI region of the hippocampus of each

slice was counted.

20   The results are shown in Table 4. The nerve

cell density in the CAI region of the hippocampus

was 287/mm in the normal (pseudo-operation) group

and that of the control group was as small as 21/mm.

Namely, a serious disappearance of the cell was

25   caused by the 5-min ischemia. On the other hand,

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when the compound of the present invention was administered, the nerve cell density was increased to prove the effect thereof in protecting the cells from the disorder.

Table 4   Effect of protecting the cells
from disorder after ischemia

Compound used	Dose (mg/kg, p.o.)	Number of cases	Nerve cell density (number/mm)
Normal group	—	6	287 ± 6
Control group	—	16	21 ± 10
Compound of Example 12	3	8	62 ± 26
	10	10	75 ± 32
	30	10	83 ± 32
Compound of Example 73	10	7	69 ± 21
	30	5	49 ± 8
Compound of Example 74	30	8	62 ± 5

Claims:

1.   Cyclic amine derivatives of the general formula
or pharmacologically acceptable salts thereof:
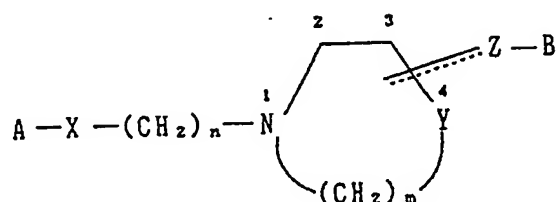
wherein A represents a substituted or unsubstituted phenyl, pyridyl or thienyl group, substituted or unsubstituted naphthyl, tetralyl, quinolyl, benzofuranyl, quinazolyl or benzothienyl group or a group of the formula:
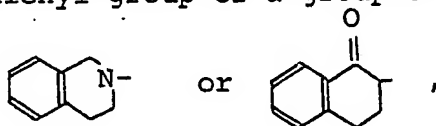
X represents a group of the formula: $-CH_2-$,

$\underline{n}$ represents an integer of 0 to 4,

$\underline{m}$ represents an integer of 1 to 3,

Y represents a carbon or nitrogen atom,

Z represents a group of the formula: $-CH_2-$

$\overset{O}{\underset{\|}{-C}}-,\ \overset{OR^1}{\underset{|}{-CH}}-$ in which R^1 is a hydrogen atom or a lower alkyl, acyl, arylalkyl or heteroarylalkyl

group, $-\overset{\overset{\text{Hal}}{|}}{\text{CH}}-$ in which Hal is a halogen atom,

=CH-, [benzene ring with $=\overset{|}{\text{C}}-$ at top and Hal at bottom] in which Hal is a halogen atom,

[benzene ring with $-\overset{|}{\text{CH}}-$ at top and Hal at bottom] in which Hal is a halogen atom or

[ring structure with $-\overset{|}{\text{CH}}-$, N, O= and =O] ,

the symbol "‐‐‐‐‐‐‐" between Y and Z represents
a single or double bond,

the group of the formula: "‐‐‐‐‐‐‐ Z-B" is
bonded with the ring in the above formula at the
3- or 4-position, and

B represents a phenyl or naphthyl group which
may be substituted with one or two substituents
which may be the same or different and which
are selected from the group consisting of
halogens, lower alkyl groups and lower alkoxy
groups.

2. Cyclic amine derivatives and pharmacologically
acceptable salts thereof according to Claim 1,
wherein A is a substituted or unsubstituted phenyl

group.

3.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a substituted or unsubstituted naphthyl group.

4.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a substituted or unsubstituted phenyl group and X is a group of the formula: $-\overset{\overset{\displaystyle O}{\|}}{C}-$.

5.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a substituted or unsubstituted naphthyl group and X is a group of the formula: $-\overset{\overset{\displaystyle O}{\|}}{C}-$.

6.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a substituted or unsubstituted phenyl group, X is a group of the formula: $-\overset{\overset{\displaystyle O}{\|}}{C}-$ and $\underline{n}$ is 1.

7.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a substituted or unsubstituted naphthyl group, X is a group of the formula: $-\overset{\overset{\displaystyle O}{\|}}{C}-$ and $\underline{n}$ is 1.

8.   Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1,

wherein A is a substituted or unsubstituted naphthyl

group, X is a group of the formula: $-\overset{\overset{\textstyle O}{\|}}{C}-$, $\underline{m}$ is 2,

Y is a carbon atom, Z is a group of the formula:

$-CH_2-$ and B is a phenyl group substituted with a

halogen.

9.   Cyclic amine derivatives and pharmacologically

acceptable salts thereof according to Claim 1,

wherein A is a substituted or unsubstituted naphthyl

group and X is a group of the formula: $-CH_2-$.

10.   A cyclic amine derivative or a pharmacologically

acceptable salt thereof according to Claim 1, which

is 2-{2-[4-(p-fluorobenzyl)piperidinyl]ethyl}naphthalene.

11.   A cyclic amine derivative or a pharmacologically

acceptable salt thereof according to Claim 1, which

is 2-(4-benzylpiperidinyl)-2'-acetonaphthone.

12.   A cyclic amine derivative or a pharmacologically

acceptable salt thereof according to Claim 1, which

is 2-[4-bis(4-fluorophenyl)methylene-1-piperidinyl]-

2'-acetonaphthone.

13.   A cyclic amine derivative or a pharmacologically

acceptable salt thereof according to Claim 1, which

is 4-(1-naphthonyl)piperidinyl-3',4'-dimethylaceto-

phenone.

14.   A cyclic amine derivative or a pharmacologically

acceptable salt thereof according to Claim 1, which

is 1-[3-(p-fluorobenzoyl)piperidinyl]-2'-aceto-
naphthone.

15. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 2-[4-(α-benzyloxy-p-fluorobenzyl)piperidinyl]-
2'-acetonaphthone.

16. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 2-[4-(α-acetoxy-p-fluorobenzyl)piperidinyl]-2'-
acetonaphthone.

17. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 4-(4-p-fluorobenzoyl)piperidinyl-6,7-dimethoxy-
isoquinoline.

18. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 4-{2-[4-(p-fluorobenzoyl)piperidinyl]ethyl}quina-
zoline.

19. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 1-(2-naphthyl)-1-[4-(p-fluorobenzoyl)piperidinyl]-
2-diethylaminoethane.

20. A cyclic amine derivative or a pharmacologically
acceptable salt thereof according to Claim 1, which
is 2-[4-(α-succinimido-p-fluorobenzyl)piperidinyl]-

2'-acetonaphthone.

21. A cyclic amine derivative or a pharmacologically acceptable salt thereof according to Claim 1, which is 2-[4-(p-fluorobenzoyl)piperidinyl]-2'-aceto-naphthone.

22. Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a naphthyl group, X is a group of the formula: $-CH_2-$, $\underline{n}$ is 1, $\underline{m}$ is 2, Y is a carbon atom and ------- Z-B is a benzyl group in the 4-position.

23. Cyclic amine derivatives and pharmacologically acceptable salts thereof according to Claim 1, wherein A is a naphthyl group, X is a group of the

formula:
$$\overset{O}{\underset{\parallel}{-C-}}$$, $\underline{n}$ is 1, Y is a carbon atom and

------- Z-B is a group of the formula: $=CH-\langle\bigcirc\rangle-F$

in the 4-position.

24. A process for producing cyclic amine derivatives of the following general formula and pharmacologically acceptable salts thereof:
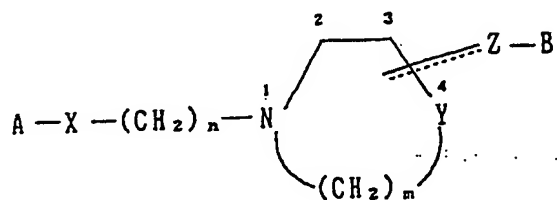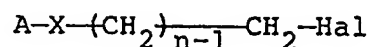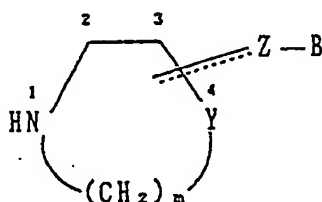
wherein A, X, $\underline{n}$, $\underline{m}$, Y, Z and B are as defined above,

characterized by reacting a halide of the general
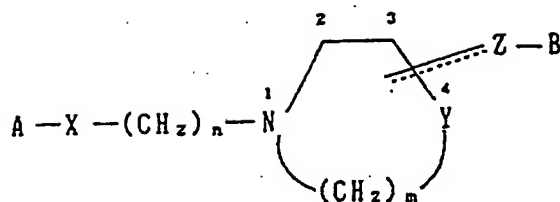
formula:

$$A-X-(CH_2)_{n-1}-CH_2-Hal$$

wherein Hal represents a halogen atom and A,

X and $\underline{n}$ are as defined above,

with a compound of the general formula:

wherein $\underline{m}$, Z, B and Y are as defined above,

to form a cyclic amine derivative of the above

general formula and, if necessary, converting this

compound into a pharmacologically acceptable salt

thereof.

25. A medicine for relieving, curing or preventing

mental symptoms due to cerebral vascular disorders,

which contains as active ingredient a cyclic amine

derivative of the following general formula or a

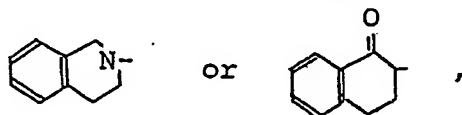pharmacologically acceptable salt thereof:

$$A-X-(CH_2)_n-N \underset{(CH_2)_m}{\overset{\underset{2}{\overbrace{\qquad}} \underset{3}{} }{\diagdown}} \overset{Z-B}{\underset{Y}{\diagup}}$$
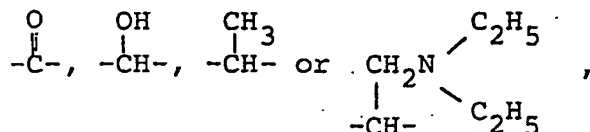
wherein A represents a substituted or unsub-
stituted phenyl, pyridyl or thienyl group,
substituted or unsubstituted naphthyl,
tetralyl, quinolyl, benzofuranyl, quinazolyl
or benzothienyl group or a group of the formula:

or

,

X represents a group of the formula: $-CH_2-$,

$-\overset{O}{\overset{\|}{C}}-$, $-\overset{OH}{\overset{|}{CH}}-$, $-\overset{CH_3}{\overset{|}{CH}}-$ or $CH_2N\overset{C_2H_5}{\underset{C_2H_5}{\diagup}}$,
$\overset{|}{\underset{-CH-}{}}$

n represents an integer of 0 to 4,

m represents an integer of 1 to 3,

Y represents a carbon or nitrogen atom,

Z represents a group of the formula: $-CH_2-$,
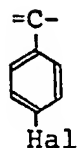
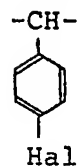$-\overset{O}{\overset{\|}{C}}-$, $-\overset{OR^1}{\overset{|}{CH}}-$ in which R^1 is a hydrogen atom or a

lower alkyl, acyl, arylalkyl or heteroarylalkyl

group, $-\overset{Hal}{\overset{|}{CH}}-$ in which Hal is a halogen atom, $=CH-$,
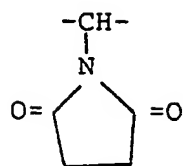
=C-

Hal

in which Hal is a halogen atom,

-CH-

Hal

in which Hal is a halogen atom, or

-CH-
|
N

O=⟨ ⟩=O

the symbol "▭" between Y and Z represents

a single or double bond,

the group of the formula: "▭ Z-B" is

bonded with the ring in the above formula at

the 3- or 4-position, and

B represents a phenyl or naphthyl group which

may be substituted with one or two substituents

which may be the same or different and which

are selected from the group consisting of

halogens, lower alkyl groups and lower alkoxy

groups.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³
According to International Patent Classification (IPC) or to both National Classification and IPC
Int.Cl⁴   C07D211/14, 211/18, 211/22, 211/32, 211/70, 295/18, 401/06, 405/04, 409/04, A61K31/445, 31/47,31/505

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC	C07D211/14, 211/18, 211/22, 211/32, 211/70, 295/18, 401/06, 405/04, 409/04, A61K31/445, 31/47, 31/505

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category*	Citation of Document, ¹ with indication, where appropriate of the relevant passages ⁷	Relevant to Claim No ⁸
X	JP, B1, 50-22033 (A.H. Robins Co., Inc.) 28 July 1975 (28. 07. 75) & US, A, 3576810 & DE, A, 1930818 & GB, A, 1268909	1

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search ⁷	Date of Mailing of this International Search Report ²
December 19, 1986 (19.12.86)	January 12, 1987 (12.01.87)

International Searching Authority ·	Signature of Authorized Officer ·⁵
Japanese Patent Office	

Form PCT-ISA/210 (second sheet) (October 1981)